PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/003722	07.04.2005	09.04.2004

International Patent Classification (IPC) or both national classification and IPC
A61K9/16, A61K9/20, A61K31/426, A61P3/06, A61P3/10, A61P9/00

Applicant
SMITHKLINE BEECHAM CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Authorized Officer

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 21-25,31

because:

☒ the said international application, or the said claims Nos. 21-25,31 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,15,17-19,22-24,27-29
	No:	Claims	1-3,5-14,16,20,21,25,26,30,31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-31
Industrial applicability (IA)	Yes:	Claims	1-20,26-30
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item IV

Lack of unity of invention

The set of claims comprises two inventions which are not so linked as to form a single general inventive concept (Rule 13.1 PCT).

The following groups of claims have been found dealing with two different technical problems:

1. Claims 1-15: Problem: providing uniform drug distribution in ultra-low dose drug formulations
   Solution: new method comprising mixing carrier particles with a solution of a drug and a binder.

2. Claims 16-31: Problem: providing a pharmaceutical composition which is useful in the treatment of various diseases
   Solution: new pharmaceutical composition comprising a specific bioactive compound

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document/s/:

D1: WO 96/09056 A (AKZO NOBEL N.V; DE HAAN, PIETER; ZWINKELS, JOCOMINUS, ANTONIUS, MARIA) 28 March 1996 (1996-03-28)

D2: DE 197 14 024 A1 (L.A.B. GESELLSCHAFT FUER PHARMAKOLOGISCHE UNTERSUCHUNGEN MBH & CO., 89) 20 November 1997 (1997-11-20)

D3: WO 97/04750 A (SMITHKLINE BEECHAM PLC; NAPPER, JAMES, ALBERT; MORTIMER, NEIL; O'BRIEN) 13 February 1997 (1997-02-13)

D4: MARTINEZ L ET AL: "Active layering and direct compression of sugar spheres: Content homogeneity in low-dosage tablets" PHARMACEUTICAL

TECHNOLOGY EUROPE 2001 UNITED KINGDOM, vol. 13, no. 10, 2001, page 38+40+42+44+46, XP009050684 ISSN: 0164-6826

D5: EP-A-0 735 864 (APPLIED ANALYTICAL INDUSTRIES, INC; ENDEAVOR PHARMACEUTICALS) 9 October 1996 (1996-10-09)

D6: WAN LUCY S C ET AL: "Incorporation and distribution of a low dose drug in granules" INTERNATIONAL JOURNAL OF PHARMACEUTICS (AMSTERDAM), vol. 88, no. 1-3, 1992, pages 159-163, XP002336534 ISSN: 0378-5173

D7: WO 02/096893 A (GLAXO GROUP LIMITED; BOYER, THIERRY; DAY, CAROLINE, JANE; WHITEHEAD, A) 5 December 2002 (2002-12-05)

D8: US-B1-6 518 290 (SIERRA MICHAEL LAWRENCE) 11 February 2003

The method and composition according to independent claims 1 and 14 are not novel (Art.33(2) PCT) in view of prior art disclosures which can be taken from D1, D2, D4, D5 and D6. Reference is made to the passages cited in the ISR for the respective documents. Said documents all deal with low dose drug formulations having uniform drug distribution prepared by a method including mixing a solution of the drug and a binder with carrier particles. The obtained mixture is most usually further mixed with tabletting agents and compressed into low unit dose tablets.

Also the dependent claims 2-13 and 15 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, would render the claimed subject-matter novel and/or inventive (Art.33(2)-(3) PCT).

The specific embodiments are known or at least suggested by the state of the art disclosed in D1-D6. Uniform distribution of ultra-low doses below 100 µg and/or below 0,005% w/w are disclosed in e.g. D1, D2 and D3. Although D3 suggests that the addition of a binder is not particularly necessary, the addition of binder can however not be considered an inventive feature as compared to D3. It is merely an obvious alternative, which a skilled person would select, especially having regard to the methods disclosed in D1, D2, D4, D5 and D6, which all suggest to add a binder in the drug solution, e.g. in order to improve adhesion of the drug to the carrier particles. Also, the ratio of drug/binder solution to carrier used in the state of the art falls within the claimed range. Mixing in a high shear mixer is

known from e.g. D1 and D3. Specific indications of RSD percentage are given e.g. in D4 and D6. The low dose formulations prepared according to the remaining documents, however, are likely to achieve a content uniformity with similar RSD %, since the disclosed preparation methods do not substantially differ from the presently claimed method. None of the additionally claimed features appears to bring a solution to any specific problem, as compared to the state of the art, which solution would involve an inventive step. Application of the claimed method to a specific bioactive compound, such as the compound defined in present claim 15 is not considered to involve an inventive step, since the methods disclosed in the state of the art are basically taught to be applicable to any kind of potent bioactive agent having sufficient solubility in the liquid binder solution. At least no unexpected effect for the claimed compound has been shown.

The composition, method and use according to independent claims 16, 21 and 26 are not novel (Art.33(2) PCT) in view of prior art disclosures which can be taken from D7 and D8. Reference is made to the passages cited in the ISR for the respective documents. Said documents disclose a medical dosage form comprising compound (1) at a daily dose of 20 µg as the lower limit, thus anticipating the claimed range. Medical application of the compound (1) as PPAR ligand in the treatment of PPAR mediated diseases is also disclosed in D7 and D8.

The dependent claims 17-20, 22-25 and 27-31 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, would render the claimed subject-matter novel and/or inventive (Art.33(2)-(3) PCT). D7 and D8 suggest to administer compound (1) in a daily amount which ranges typically from 20 µg to 5 g. This daily dose may be administered as a single dose or as divided sub-doses, e.g. two, three, four or more sub-doses. Accordingly a dosage form comprising less than 20 µg of compound (1) is implicitly suggested by D7 and D8, e.g. 10 µg when divided in two sub-doses, 5 µg when divided in four sub-doses, etc. Furthermore, it should be noted that the present application does not provide any experimental data on the therapeutic efficiency of ultra-low doses below 20 µg daily, which is the lower limit suggested by D7 and D8. Also, no comparison with higher daily doses (typically 20 µg or more as suggested in D7/D8) is provided in terms of relative efficiency. Hence, the claimed lower limit of 1 µg daily is merely considered an obvious alternative to the range defined in D7 and D8 with corresponding lower therapeutical effect, e.g. for subjects in need of only a very low

therapeutical effect. Under such conditions no inventive step can be seen.

The subject-matter defined in claims 1-20 and 26-30 is considered to be industrially applicable and accordingly meets the requirements of Art.33(4) PCT.